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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,641	10/07/2005	Russell Gene Higuchi	21634-US2	1928
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Roche Molecular Systems, Inc. Patent Law Department 4300 Hacienda Drive Pleasanton, CA 94588			EXAMINER BAUSCH, SARAE L	
			ART UNIT 1634	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/552,641

Applicant(s)

HIGUCHI ET AL.

Examiner

SARAE BAUSCH

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 December 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-78 is/are pending in the application.
- 4a) Of the above claim(s) 8-10, 28-31 and 45-78 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7, 11-27 and 32-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 October 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 02/07.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. This action is in response to applicants correspondence mailed 12/18/2007.

Election/Restrictions

2. Applicant's election with traverse of group I, SNP FRZB_G19524A in the reply filed on 12/18/2007 is acknowledged. The traversal is on the ground(s) that the elected specific polymorphism or combination of polymorphisms is an election of species. The response asserts that separate, non-overlapping iterations of the claimed invention using different species within the genus are possible and this could be said for every list of species within a genus claim and does not actually make the restriction not a species election. The response that the field of search is the same in direct contradiction to the examiner's statement. The response asserts that different species are simply different polymorphisms of the same gene related to the same condition and predisposition, will typically be cited in publications from the same type of searches and the assertion that different species requires different field of search is absurd. This is not found persuasive because applicant does not point to specific reasons as to why the restriction should be a species requirement and not a restriction requirement. The restriction is proper as each subcombination set forth in the restriction requirement mailed 07/18/2007 are distinct, there is no evidence on the record to suggest that they are obvious variants of one another, are separately usable as evidence by their presentation in the alternative within the claims, and there would be a serious burden if restriction is not required because the inventions require a different field of search. With regard to applicant assertion that the field of search is the same for each species is not found persuasive as the complex nature of the claimed material requires searching each polymorphism in a separate query of electronic databases and a search

for a method of use of one polymorphism is not co-extensive with a method for use of another polymorphisms and subsequently the search and examination of multiple polymorphisms poses and enormous and serious burden on the examiner. Therefore, the restriction is maintained.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 8-10, 28-31, 45-78 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/18/2007.
4. Currently, claims 1-7, 11-27, and 32-44 are under examination. The G19524A allele for claims 7, 27, and 44 is under examination.

Drawings

5. The drawings are acceptable.

Specification

6. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.
7. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. For example page 13 line 33-34, page 40 lines 8-10, and page 48 lines 32.

Claim Rejections - 35 USC § 112-Description

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-7, 11-27, and 32-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

The rejected claims are broadly drawn to methods for a determining obesity or osteoporosis comprising detecting presence of one osteoporosis or obesity-related polymorphism in a frizzled related protein gene in a nucleic acid sample from an individual. The rejected claims provide no structural limitation regarding an osteoporosis or obesity related polymorphism in a frizzled related protein gene.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis and detection of an enormous and wide variety of nucleic acid sequences. The claims are broadly drawn to a method that encompass a plurality of nucleic acids an extremely large genus of polymorphic variants of any frizzled related protein gene (encompasses Frzb1-4, secreted frizzled related genes, etc) with any nucleotide content (A

or G or C or T) at any position within any frizzled related gene in any organism. Thus the claims encompass the detection of any of the many different nucleic acids wherein the nucleic acid sequence is correlated with an association of disease. Nucleic acids of such a large genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The specification of the instant application discloses one nucleic acid sequence, SEQ ID No. 1 by their complete structure. The specification lists polymorphisms of SEQ ID No. 1, see table 1, however the specification only discloses 11 polymorphisms within SEQ ID No. 1 of which only one is associated with BMI (see table 4) and one is associated with vertebral fracture (see table 5), and therefore the specification does not provide a representative number of polymorphisms in a frizzled related protein gene in an individual that are associated with obesity or osteoporosis. Furthermore, the specification does not disclose the nucleic acid or amino acid structure for other frizzled-related proteins or secreted frizzled related proteins. For example, the specification teaches SEQ ID No. 1 however the specification does not disclose the genomic sequence of other frizzled-related proteins or secreted frizzled related proteins. Furthermore there are 128 known polymorphisms for FRZB (See gene card, page 9). In addition, there are currently eight known species of FRZB (see gene card, page 7). The specification does not provide any disclosure as to the association of a polymorphism in each of these genes to diagnosis of obesity or osteoporosis.

The instant specification provides the sequence of SEQ ID No. 1 which corresponds to the frizzled-related protein 1, secreted frizzled-related protein 3 and 11 polymorphic variations of

SEQ ID no. 1, of which only 2 variants show an association with either obesity or osteoporosis (see table 4 and 5). Furthermore, the frizzled-related protein 1 has 128 known polymorphisms (see genecard, pg. 9) and the specification does not provide a representative number of polymorphic variants within the frizzled-related protein 1 in any species that are associated with obesity or osteoporosis.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification provides only the polymorphic sequences of SEQ ID no. 1. The specification does not provide any characteristics that would allow one to identify any particular portions or fragments or variants of the disclosed sequence that would allow for the diagnosis of any type of obesity or osteoporosis based on detection of the non-disclosed gene.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because of the lack of any analysis regarding polymorphisms of the frizzled related gene and association with obesity or osteoporosis, one of skill in the art

cannot envision the detailed chemical structure of the nucleic acid encompassed by the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method for detecting the presence of a frizzled related protein gene polymorphism and its associated with either obesity or osteoporosis in an individual.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Claim Rejections - 35 USC § 112- Enablement

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-7, 11-27, and 32-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and the breadth of the claims

The claims are drawn to a method for the determining an individual's risk for obesity or osteoporosis comprising detecting presence of at least one obesity related or osteoporosis related polymorphism in a frizzled related protein gene (FRZB) in a nucleic acid sample in an individual. The claims are further drawn to determining an increased or decreased risk of obesity or osteoporosis in comparison to an individual without an obesity or osteoporosis related polymorphism. Additional claims include polymorphisms that are predisposing or protective in FRZB. The claims are further drawn to presence of a polymorphism inherited from an individual's parent. Additional claims are drawn to detecting the presence of the polymorphism G19524A allele to determine risk of obesity or osteoporosis in an individual

The rejected claims encompass analysis of any individual, including human and non-human. The rejected claims encompass any type of osteoporosis. The rejected claims encompass any frizzled related protein gene, including secreted frizzled related protein genes.

The nature of the claims requires knowledge of a correlation between detection of the presence of a FRZB1 polymorphism and predisposition to develop osteoporosis or risk for obesity.

The invention is in a class of inventions which the CAFC has characterized as “the unpredictably arts such as chemistry and biology” (*Mycolgen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Guidance in the Specification and Working Examples

The specification teaches the present invention is related to methods for detecting an individuals risk for obesity and/or osteoporosis by identifying the presence of at least one polymorphism in the FRZB gene (See pg. 1, lines 5-10). The specification teaches an individuals risk for obesity can be either an increase or decreased risk as compared to an individual without the at least one polymorphism (see pg. 3, lines 5-10). The specification teaches that the at least one polymorphism can be any suitable polymorphism (see pg. 3, lines 10-11). The specification teaches that the nucleic acid sample can be detected by any of the variety of methods known in the art (see pg. 3, lines 29-31). The specification teaches that the individual can be any mammal, including human and belong to any race or population (See pg. 23, lines 21-22). Although detection of nucleic acids and detection of polymorphisms is routine in the art, predictably correlating any polymorphism in the FRZB gene with risk for osteoporosis and/or obesity in any human or non-human individual is unpredictable and the specification does not predictably correlate a representative number of polymorphisms in the FRZB gene with obesity or osteoporosis in any human or non-human individual.

The specification teaches the invention provides for detecting an individual's increased or decreased risk for obesity or osteoporosis by detecting the presence of one or more FRZB SNPs wherein the presence indicated individuals increased or decreased risk for obesity or osteoporosis (see pg 27, lines 9-20). The specification does not provide any guidance on how the presence of one FRZB SNP can determine both an increased and decreased risk of obesity or osteoporosis. Furthermore, the specification does not provide any guidance on how one polymorphism can be both protective as well as predisposing to obesity and osteoporosis. Additionally, the specification does not provide any guidance on polymorphisms inherited from an individual parents and their association with obesity or osteoporosis.

The specification demonstrates a working example of pooling DNA samples from patients with either hip fracture (275 patients), vertebral fracture (262 patients), low bone mineral density (276 patients), control (278 patients), along with patients with a high BMI (141 samples) and low BIM (82 samples) (see pg. 49, lines 10-16). The specification asserts that a significant association between an increased BMI and FRZB_G19524A SNP was demonstrated ($p<.05$) and the A allele of G19524 was associated with increased BMI (see pg. 50, lines 13-18). The specification asserts that a lesser association between increased incidence of hip fracture and FRZB_G19524A SNP ($p<.01$) and asserts that the G allele of G19524A was demonstrated to be associated with increases incidence of hip fracture (see pg. 50 lines 23-30). However, the specification provides is no data for the association of G19524A allele and its association with increase, decrease, protective, or predisposition for osteoporosis.

Table 4 presents the data for the association of the G195424A allele and high and low BMI in women. Table 4 presents two p values, overall distribution of G19524A of $p=.0051$ and

model where 19524A is recessive allele, $p=.0032$, however it is unclear if the p values represent the association of the homozygous or heterozygous G allele or A allele of 19524.

The data presented in examples 1-2 does not demonstrate a representative number of polymorphisms within the FRZB gene that are predictably associated with osteoporosis or obesity and therefore does not provide any guidance on how to predictably correlate any polymorphisms, including G19524A with increased, decreased, protective, and predisposition to obesity or osteoporosis as the specification does not teach either the G or the A allele as being predictably associated with increased, decreased, protective and predisposing to obesity or osteoporosis.

The specification does not teach any analysis of any non-human individuals. The specification teaches that FRZB gene is a small component of the complex system of genes associated with obesity and osteoporosis and the effect of the FRZB locus is expected to be variable. The specification teaches that other factors such as eating habits, exercise, diet, general health, and the presence of associated diseases may exert dominating effects which in some cases may mask the effect of the FRZB genotype. The specification further teaches that the allele frequencies at other loci relevant to weight and bone related diseases differ between populations and thus populations exhibit different risks for such diseases and therefore it is expected to that the effect of the FRZB genotype may be different in some populations (See pg. 53, lines 1-15). Therefore it can be concluded from the specification that it is unpredictable to correlate any one polymorphism in the FRZB gene in any individual with obesity or osteoporosis, as both disorders involve a complex system of genes, other associated diseases and environmental

factors may dominate the effects of the genotype, and the effect of the FRZB genotype may be different in different populations.

The following is unclear from the teaching in the specification. The specification does not teach which polymorphisms of the FRZB gene are predictably correlative to increased and decreased risk of obesity or osteoporosis. The specification provides no guidance on how the same allele can be both an indicator for increased and decreased risk as well as both protective and diagnostic for obesity and osteoporosis. The specification does not provide reasonable guidance which allele, G or A, at 19524 homozygous or heterozygous is statistically associated with high BMI in females. The specification does not provide any analysis of any polymorphism within the FRZB gene and its association with increased BMI within a male population. The specification provides no statistically significant data to provide guidance on the association of the G or A allele of 19524 with osteoporosis. Although the specification shows a potential relationship of high BMI in women with the presence of the A allele at position 19524, the specification does not clearly provide guidance that demonstrates the presence of A allele, either homozygous or heterozygous at position 19524 is predictably associated with increased risk of high BMI in women.

The unpredictability of the art, level of skill in the art, and the state of the prior art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach any association between any polymorphism in FRZB gene and predisposition in any individual for obesity or osteoporosis, or determination of 19524 allele in obesity or osteoporosis.

It is unpredictable as to whether or not a sequence comprising FRZB and the position of 19524 as a SNP exists in any non-human organisms, and whether or not detection of a polymorphism in such a sequence in any other organism would be predictive of the risk of obesity or osteoporosis. For example, Mummidi et al. (2000). Mummidi et al. teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates. Notably, the reference teaches that the substantial interspecies sequence variation is observed for the cis-regulatory regions of the CCR5 gene (p. 18949, right column, 1st full paragraph). Thus it is entirely unpredictable as to whether or not any polymorphism, including the specifically claimed polymorphic positions would be associated with obesity or osteoporosis.

Because the claims are drawn to methods that encompass the analysis of any polymorphism of FRZB gene, it is relevant to note that there are multiple polymorphic positions identified in FRZB. A Gene Card search of FRZB gene indicates that there are 128 SNPs of FRZB gene (see page 9 of Gene Card). The instant specification does not teach any association of these 128 polymorphisms with obesity or osteoporosis.

Additionally, the prior art teaches that there are many parameters that need to be evaluated prior to using a genetic test to determine a disease and that these parameters yield gaps in information that are needed to complete a thorough screening of a genetic test. Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated

must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong.

Furthermore, Ionnidis (Plost Med, 2005, 2(8):e124) teach that most published research findings are false. Ionnidis et al. teach that ill-founded strategy of claiming conclusive research finding solely on the basis of a single study assed by formal statistical significance represented and summarized by p values (see pg. 0696, 2nd column, 1st full para.) Ionnidis et al. teach that research findings are likely to be true that in fields that undertake large studies, such as randomized controlled trials (several thousand subjects randomized) than in small studies such as sample sizes 100 fold or smaller (see pg. 0697, 3rd column, 2nd full para.) Ionnidis et al. teaches that what matters is the totality of evidence and that statistical significance of a single study only gives a partial picture (see pg. 0701, 1st column). Additionally, Hattersley et al. (Lancet, 2005, vol 366, pp. 1315-1323) teaches that the key quality in an association study is sample size (see

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page 1318, 2nd column, 1st full paragraph). Hattersley et al. teach that sample sizes of thousands are needed to detect variants that are common but have low relative risk and teach that allelic odds ratio of 1.1 to 2.0 requires the number of controls to be in thousands (see page 1318, 2nd column, 1st full paragraph and table 3). Hattersley et al. teach that apparent studies in identifying interesting associations with studies much smaller than implied by table 3 (in the thousands) might suggest that calculations are too pessimistic and small initial studies rarely find the correct result and even when they do they are likely to overestimate the true effect size (see page 1318, 1st column, 1st full paragraph). Hattersley et al. further teaches that emphasis has been on the need for greater stringency in the association studies in order to prove a given association and suggest a p value of 5×10^{-8} , however arguments from Bayesian perspective suggest that 5×10^{-5} should be sufficient to constrain the false discovery rate. It is further relevant to point out that Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

Additionally, post filing art Ikegawa et al. (Curr Opin Rheumatol 2007 19(5):429-434) teaches that the association of two polymorphisms within the FRZB is not associated with osteoporosis in all population s (See pg. 2, FRZB). Ikegawa teaches that two variants increase the risk of knee and hip osteoarthritic in Caucasian women but not in men. Ikegawa et al.

teaches that in a Spanish population no direct replication of the association of the same two polymorphisms was obtained (see pg. 2 last para). Therefore there is evidence in the post filing art that polymorphisms within the FRZB gene in different populations are not predictably associated with osteoporosis.

Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate any polymorphism within the FRZB gene with osteoporosis or obesity or determine the association of 19524 with obesity or osteoporosis, as the specification does not teach a large sample size, p values less than .05 or confidence levels greater than 95% for a representative number of polymorphisms within FRZB. The specification only teaches a large sample size with statistically significant data for the analysis of an association between high BMI in women and the position 19524 however the specification does not clearly teach the allele associated with high BMI. The specification does not teach statistically significant data ($p < .05$) for the association of the allele at position 19524 and osteoporosis. Furthermore, the specification does not characterize the individuals as having additional disorders that could contribute to obesity or osteoporosis.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to association of any polymorphism in the FRZB gene with osteoporosis or obesity in “any” species the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different populations and familial studies for each of the polymorphisms of the FRZB (128 polymorphisms known) to determine if in fact there was either an association between the polymorphism in an individuals and obesity or osteoporosis and to

determine if 19524 was involved with obesity, BMI index, osteoporosis. The results of such a study are unpredictable as evidence by the post filing art (which reflects the current state of the art) and the teachings in the specification. In the instant case, it would be unpredictable as to whether or not polymorphisms of FRZB would be responsible for determining the predisposition to obesity or osteoporosis in any individual as well as unpredictable as to whether the G or A allele of 19524 is indicative increased and decreased risk along with being both protective and predisposing to obesity and osteoporosis. In order to practice the invention as broadly as it is claimed, the skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictable determine a susceptibility to all or any osteoporosis and obesity. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, such analysis is replete with unpredictable experimentation and is considered undue.

Conclusion

12. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Sarae Bausch/
Examiner, Art Unit 1634